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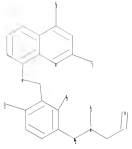
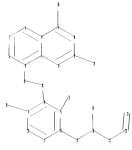




chain nodes :
17 18 19 20 22 23 26 27 29 31 32
ring nodes :
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16
ring/chain nodes :
21
chain bonds :
6-17 7-26 9-27 13-31 14-18 15-32 16-19 17-18 19-20 20-21 20-29 21-22
22-23
ring bonds :
1-2 1-6 2-3 3-4 4-5 4-7 5-6 5-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14
14-15 15-16
exact/norm bonds :

6-17 7-26 9-27 13-31 15-32 17-18 19-20 20-21 20-29 22-23
exact bonds :
14-18 16-19 21-22
normalized bonds :
1-2 1-6 2-3 3-4 4-5 4-7 5-6 5-10 7-8 8-9 9-10 11-12 11-16 12-13 13-14
14-15 15-16
isolated ring systems :
containing 1 : 11 :

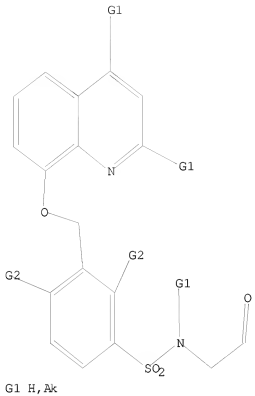
G1:H,Ak

G2:O,S,CN,X,Ak

Match level :
1:Atom 2:Atom 3:Atom 4:Atom 5:Atom 6:Atom 7:Atom 8:Atom 9:Atom 10:Atom
11:Atom 12:Atom 13:Atom 14:Atom 15:Atom 16:Atom 17:CLASS 18:CLASS 19:CLASS
20:CLASS 21:CLASS 22:CLASS 23:CLASS 26:CLASS 27:CLASS 29:CLASS 31:CLASS
32:CLASS

L1 STRUCTURE UPLOADED

=> d l1
L1 HAS NO ANSWERS
L1 STR



G1 H,Ak

G2 O,S,CN,X,Ak

Structure attributes must be viewed using STN Express query preparation.

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=> s l1 full
L3          339 SEA SSS FUL L1

=> file ca
COST IN U.S. DOLLARS                                SINCE FILE      TOTAL


=> s l3
L4            9 L3

=
=> d ibib abs fhitstr 1-9

L4   ANSWER 1 OF 9  CA  COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER:        148:299502  CA
TITLE:                   MEN16132, a kinin B2 receptor antagonist, prevents the
                         endogenous bradykinin effects in guinea-pig airways
AUTHOR(S):               Valenti, Claudio; Cialdai, Cecilia; Giuliani, Sandro;
                         Tramontana, Manuela; Quartara, Laura; Maggi, Carlo
                         Alberto
CORPORATE SOURCE:        Pharmacology Department, Menarini Ricerche S.pA.,
```

Florence, 50131, Italy
SOURCE: European Journal of Pharmacology (2008), 579(1-3), 350-356
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB Kinins have been suggested to be involved in human airway diseases such as asthma and rhinitis. MEN16132 is a non-peptide kinin B2 receptor antagonist able to inhibit the responses produced by i.v. bradykinin into the airways, as bronchoconstriction and microvascular leakage; we tested the effect of MEN16132 on endogenously generated bradykinin through the dextran sulfate-induced contact activation of kinin-kallikrein cascade in guinea-pigs. After dextran sulfate administration (1.5 mg/kg i.v.), the pulmonary insufflation pressure was monitored and the microvascular leakage of upper and lower airways was assessed using Evans blue as tracer of plasma protein extravasation. Our results demonstrated that topical MEN16132 strongly inhibited the dextran sulfate-induced bronchoconstriction (0.3 mM solution aerosol for 5 min) and plasma protein extravasation in both lower airways (3-10 μM solution aerosol for 5 min) and nasal mucosa (0.3 nmol/nostril); Icatibant, the peptide antagonist of kinin B2 receptor, exerted a 3-30-fold less potent inhibitory effect than MEN16132. We conclude that local application of MEN16132 into the airways abolishes the responses produced by the endogenous generation of bradykinin and it can be useful as new pharmacol. tool to check the role of kinins in human diseases.

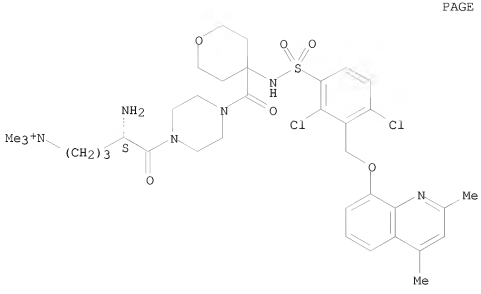
IT 869880-33-1, MEN16132
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(MEN16132, a kinin B2 receptor antagonist, prevents the endogenous bradykinin effects in guinea-pig airways)

RN 869880-33-1 CA

CN 1-Piperazinepentanaminium, δ-amino-4-[[4-[[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]tetrahydro-2H-pyran-4-yl]carbonyl]-N,N,N-trimethyl-ε-oxo-, chloride, hydrochloride (1:1:1), (δS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

● Cl⁻

● HCl

REFERENCE COUNT: 55 THERE ARE 55 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 2 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:338134 CA
TITLE: Design and synthesis of novel sulfonamide-containing bradykinin hB2 receptor antagonists. 2. synthesis and structure-activity relationships of α,α-cycloalkylglycine sulfonamides
AUTHOR(S): Fattori, Daniela; Rossi, Cristina; Fincham, Christopher I.; Caciagli, Valerio; Catrambone, Fernando; D'Andrea, Piero; Felicetti, Patrizia; Gensini, Martina; Marastoni, Elena; Nannicini, Rossano; Paris, Marielle; Terracciano, Rosa; Bressan, Alessandro; Giuliani, Sandro; Maggi, Carlo A.; Meini, Stefania; Valenti, Claudio; Quartara, Laura
CORPORATE SOURCE: Menarini Ricerche, Pomezia (Rome), 00040, Italy
SOURCE: Journal of Medicinal Chemistry (2007), 50(3), 550-565 CODEN: JMCMAR; ISSN: 0022-2623
PUBLISHER: American Chemical Society
DOCUMENT TYPE: Journal

LANGUAGE: English
OTHER SOURCE(S): CASREACT 146:338134
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

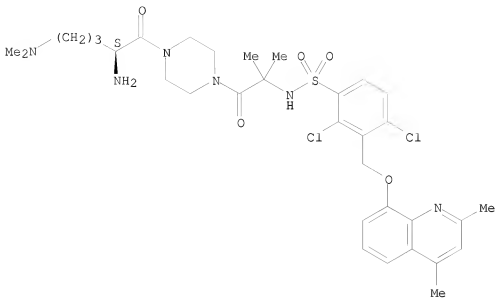
AB Recently, the design and synthesis of a class of selective nonpeptide bradykinin (BK) B2 receptor antagonists (J. Med. Chemical 2006, 3602-3613) was reported. This work led to the discovery of MEN 15442 (I), an antagonist with subnanomolar affinity for the human B2 receptor (hB2R), which also displayed significant and prolonged activity in vivo (for up to 210 min) against BK-induced bronchoconstriction in the guinea-pig at a dose of 300 nmol/kg (it), while demonstrating only a slight effect on BK-induced hypotension. Herein, the further optimization of this series of compds. aimed at maximizing the effect on bronchoconstriction and minimizing the effect on hypotension, with a view to developing topically delivered drugs for airway diseases, is described. It was found that MEN 16132 (II), after intratracheal or aerosol administration, inhibited, in a dose-dependent manner, BK-induced bronchoconstricton in the airways, while showing minimal systemic activity. This compound was selected as a preclin. candidate for the topical treatment of airway diseases involving kinin B2 receptor stimulation.

IT 635695-78-2, MEN 15442
RL: PAC (Pharmacological activity); BIOL (Biological study)
(preparation, bradykinin B2 receptor antagonistic activity and SAR of cycloalkylglycine sulfonamides)

RN 635695-78-2 CA

CN Benzenesulfonamide, N-[2-[4-[(2S)-2-amino-5-(dimethylamino)-1-oxopentyl]-1-piperazinyl]-1,1-dimethyl-2-oxoethyl]-2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]- (CA INDEX NAME)

Absolute stereochemistry.



REFERENCE COUNT: 16 THERE ARE 16 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 3 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:288256 CA
TITLE: Comparative antagonist pharmacology at the native mouse bradykinin B2 receptor: radioligand binding and smooth muscle contractility studies
AUTHOR(S): Meini, S.; Cucchi, P.; Bellucci, F.; Catalani, C.; Giuliani, S.; Santicioli, P.; Maggi, C. A.
CORPORATE SOURCE: Department of Pharmacology, Menarini Ricerche, Florence, Italy
SOURCE: British Journal of Pharmacology (2007), 150(3), 313-320
CODEN: BJPCBM; ISSN: 0007-1188
PUBLISHER: Nature Publishing Group
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The aim was to characterize the recently discovered non-peptide antagonist MEN16132 at the mouse B22 receptor, relative to other antagonists. [3H]-BK binding expts. used mouse lung and ileum tissue membranes and antagonist potency was measured in the isolated ileum contractility assay. Two BK binding sites resulted from saturation and homologous competition expts. A role for the B1 receptor was excluded because of the poor affinity of B1 receptor ligands (pIC50 <5). MEN16132, and the other reference antagonists, inhibited only one portion of BK specific binding, and the rank order of potency was (pIC50): Icatibant (lung 10.7; ileum 10.2)= MEN11270 (lung 10.4; ileum 9.9) = MEN16132 (lung 10.5; ileum 9.9). > LF16-0687 (lung 8.9; ileum 8.8) > FR173657 (lung 8.6; ileum 8.2). BK homologous curves performed with lung membranes after treatment with the antagonist MEN16132 or Icatibant (10 nM) displayed only the low affinity site. The functional antagonism by MEN16132 (pA2 9.4) and Icatibant (pA2 9.1), towards BK (control EC50 6.1 nM) induced ileum contractions, was concentration-dependent and

surmountable, but the Schild plot slope was less than unity. In mouse tissue, radiolabeled BK recognizes two binding sites and B2 receptor antagonists can compete only for the higher affinity one. The pharmacol. profile of the novel non-peptide antagonist MEN16132 indicates that it exhibits subnanomolar affinity and potency for the mouse B2 receptor and is suitable for further characterization in in vivo pathophysiol. models.

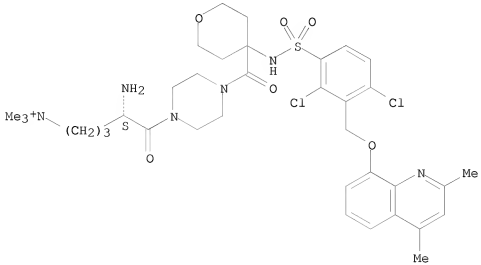
IT 869880-33-1, MEN16132
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(comparative antagonist pharmacol. at the native mouse bradykinin B2 receptor and radioligand binding and smooth muscle contractility studies)

RN 869880-33-1 CA

CN 1-Piperazinepentanaminium, δ-amino-4-[[4-[[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]tetrahydro-2H-pyran-4-yl]carbonyl]-N,N,N-trimethyl-ε-oxo-, chloride, hydrochloride (1:1:1), (δS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

● Cl^-

● HCl

REFERENCE COUNT: 28 THERE ARE 28 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 4 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 146:128654 CA
TITLE: Pharmaceutical compositions containing kinin antagonists for the the treatment of bladder diseases
INVENTOR(S): Gibson, Christoph; Hummel, Gerd; Knolle, Jochen; Reineke, Ulrich; Tradler, Thomas
PATENT ASSIGNEE(S): Jerini A.-G., Germany
SOURCE: PCT Int. Appl., 89pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2007003411	A2	20070111	WO 2006-EP6504	20060704
WO 2007003411	A3	20070518		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM, AP, EA, EP, OA				
EP 1741444	A1	20070110	EP 2005-14581	20050705
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AU 2006265266	A1	20070111	AU 2006-265266	20060704
CA 2613627	A1	20070111	CA 2006-2613627	20060704
EP 1901775	A2	20080326	EP 2006-754662	20060704
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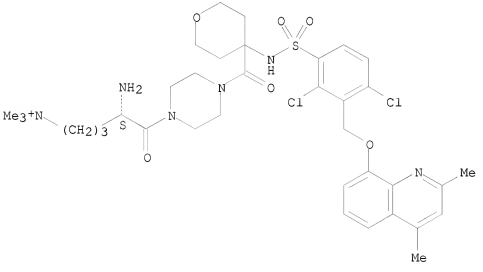
IN 2008DN00008	A	20080404	IN 2008-DN8	20080101
KR 2008025120	A	20080319	KR 2008-700150	20080103
PRIORITY APPLN. INFO.:			EP 2005-14581 A	20050705
			WO 2006-EP6504 W	20060704

OTHER SOURCE(S): MARPAT 146:128654
AB The present invention is related to the use of a kinin receptor antagonist for the manufacture of a medicament for the treatment and/or prevention of bladder dysfunction, whereby the kinin receptor is selected from the group comprising B1 and B2 receptors. For example, i.v. injections containing B1 kinin receptor R-715 and B2 receptor antagonist icatibant was found to have the effect of alleviating the overactive bladder.
IT 869939-83-3
RL: THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(pharmaceutical compns. containing kinin antagonists for treatment of bladder diseases)
RN 869939-83-3 CA

CN 1-Piperazinepentanaminium, δ-amino-4-[[4-[[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]tetrahydro-2H-pyran-4-yl]carbonyl]-N,N,N-trimethyl-ε-oxo-, (δS)- (CA INDEX NAME)

Absolute stereochemistry.



L4 ANSWER 5 OF 9 CA COPYRIGHT 2008 ACS on STN

ACCESSION NUMBER: 145:145995 CA

TITLE: Design and Synthesis of Novel Sulfonamide-Containing Bradykinin hB2 Receptor Antagonists. 1. Synthesis and SAR of α,α-Dimethylglycine Sulfonamides

AUTHOR(S): Fattori, Daniela; Rossi, Cristina; Fincham, Christopher I.; Berettoni, Marco; Calvani, Federico; Catrambone, Fernando; Felicetti, Patrizia; Gensini, Martina; Terracciano, Rosa; Altamura, Maria; Bressan, Alessandro; Giuliani, Sandro; Maggi, Carlo A.; Meini, Stefania; Valenti, Claudio; Quartara, Laura

CORPORATE SOURCE: Menarini Ricerche, Pomezia, 00040, Italy

SOURCE: Journal of Medicinal Chemistry (2006), 49(12), 3602-3613
CODEN: JMCMAR; ISSN: 0022-2623

PUBLISHER: American Chemical Society

DOCUMENT TYPE: Journal

LANGUAGE: English

OTHER SOURCE(S): CASREACT 145:145995

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB The authors report how sulfonamide-containing human B2 receptor (hB2R) antagonists were designed, synthesized, and optimized to provide a group

of products with subnanomolar affinity for the hB2R and high in vivo potency after topical administration to the respiratory tract. The series was designed on the basis of indications from the x-ray structures of the key structural motifs present in known antagonists and is characterized by the presence of an α,α-dialkyl amino acid. The first lead of the series, sulfonamide I, was submitted to extensive chemical work to elucidate the structural requirements to increase hB2 receptor affinity and antagonist potency in bioassays expressing the human B2 receptor (hB2R). The following structural features were selected: a 2,4-dimethylquinoline moiety and a piperazine linker acylated with a basic amino acid. The representative lead sulfonamide II inhibited the specific binding of [3H]BK to hB2R with a pKi of 9.4 and antagonized the BK-induced inositolphosphate (IP) accumulation in recombinant cell systems expressing the hB2R with a pA2 of 9.1. Moreover, II when administered (300 nmol/kg) intratracheally in the anesthetized guinea pig, was able to significantly inhibit BK-induced bronchoconstriction for up to 120 min after its administration, while having a lower and shorter lasting effect on hypotension.

IT 635694-96-1P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); BIOL (Biological study); PREP (Preparation)
(preparation and SAR of dimethylglycine sulfonamides as bradykinin hB2 receptor antagonists)

RN 635694-96-1 CA

CN Piperazine, 1-[(2S)-2-amino-6-(dimethylamino)-1-oxohexyl]-4-[2-[[[2,4-dichloro-3-[[(2-methyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]-2-methyl-1-oxopropyl]-, trifluoroacetate (9CI) (CA INDEX NAME)

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CRN 635694-95-0
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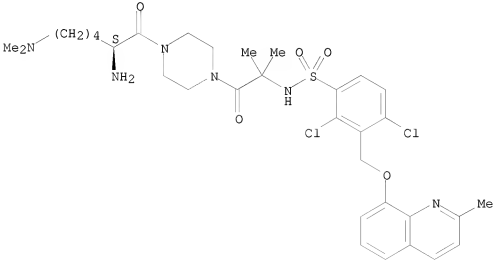
Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

REFERENCE COUNT: 35 THERE ARE 35 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 6 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:412540 CA
TITLE: Preparation of piperazine-linked amino acid derivatives with a cyclic group and a quaternary ammonium group in the alpha positions as non-peptide bradykinin antagonists with specific B2 receptor antagonistic activity
INVENTOR(S): Felicetti, Patrizia; Fincham, Christopher Ingo; Giolitti, Alessandro; Maggi, Carlo Alberto; Quartara, Laura; Rossi, Cristina
PATENT ASSIGNEE(S): Istituto Luso Farmaco d'Italia S.p.A., Italy
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006040004	A1	20060420	WO 2005-EP10412	20050927
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RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005293881	A1	20060420	AU 2005-293881	20050927
CA 2583920	A1	20060420	CA 2005-2583920	20050927
EP 1799214	A1	20070627	EP 2005-789989	20050927
EP 1799214	B1	20071226		
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CN 101039671	A	20070919	CN 2005-80034833	20050927
AT 381931	T	20080115	AT 2005-789989	20050927
US 20070281944	A1	20071206	US 2007-786041	20070410

IN 2007KN01295 A 20070720 IN 2007-KN1295 20070412
PRIORITY APPLN. INFO.: IT 2004-MI1963 A 20041015
WO 2005-EP10412 W 20050927
OTHER SOURCE(S): MARPAT 144:412540
GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Non-peptide compds. I, which have activity as specific antagonists of bradykinin (BK) B2 receptor and can be used in treating a variety of conditions in which activation of B2 receptors is involved, are disclosed [wherein: R = H or methyl; W = single bond or O; n = 3 or 4; X = H or (un)substituted amino; Y = quaternary ammonium group, and pharmaceutically acceptable salts, enantiomers and enantiomeric mixts. thereof]. For instance, ammonium chloride II was prepared as a dihydrochloride salt in multiple steps from 2,6-dichlorotoluene, 4-aminotetrahydropyran-4-carboxylic acid, 2,4-dimethyl-8-quinolinol, N-Bocpiperazine and Boc-Orn-OH. Biol. assays showed that the invented compds. have higher binding affinity in vivo (pKi = 10.3 for II) and stronger antagonistic activity in vitro (pA2 = 10.3 for II) than the structurally related analogs of patent WO03103671.

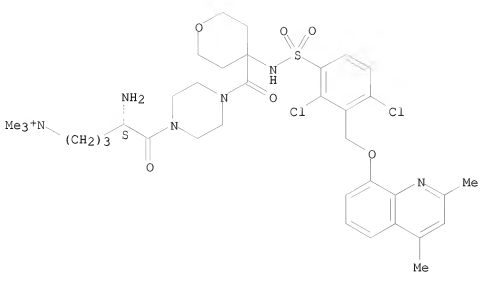
IT 883969-00-4P
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of piperazine-linked amino acid derivs. with a cyclic group and a quaternary ammonium group in the alpha positions as non-peptide, B2-selective bradykinin antagonists)

RN 883969-00-4 CA

CN 1-Piperazinepentanaminium, δ-amino-4-[[4-[[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]tetrahydro-2H-pyran-4-yl]carbonyl]-N,N,N-trimethyl-ε-oxo-, chloride, dihydrochloride, (δS)- (9CI) (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

● Cl⁻

● 2 HCl

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 7 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:64077 CA
TITLE: MEN16132, a novel potent and selective nonpeptide antagonist for the human bradykinin B2 receptor. In vitro pharmacology and molecular characterization
AUTHOR(S): Cucchi, Paola; Meini, Stefania; Bressan, Alessandro; Catalani, Claudio; Bellucci, Francesca; Santicioli, Paolo; Lecci, Alessandro; Faiella, Angela; Rotondaro, Luigi; Giuliani, Sandro; Giolitti, Alessandro; Quartara, Laura; Maggi, Carlo Alberto
CORPORATE SOURCE: Department of Pharmacology, Menarini Ricerche, S.p.A., Florence, 12A, Italy
SOURCE: European Journal of Pharmacology (2005), 528(1-3), 7-16
CODEN: EJPHAZ; ISSN: 0014-2999
PUBLISHER: Elsevier B.V.
DOCUMENT TYPE: Journal
LANGUAGE: English

AB The pharmacol. characterization of the novel nonpeptide antagonist for the B2 receptor, namely MEN16132 (4-(S)-Amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-8-quinolyloxymethyl)phenylsulfonamido]-tetrahydro-2H-4-pyranylcarbonyl}piperazino)-5-oxopentyl(trimethyl)ammonium chloride hydrochloride) is presented. The affinity of MEN16132 for the bradykinin B2 receptor has been investigated by means of competition studies at [3H]bradykinin binding to membranes prepared from Chinese Hamster Ovary (CHO) cells expressing the human bradykinin B2 receptor (pKi 10.5), human lung fibroblasts (pKi 10.5), guinea pig airways (pKi 10.0), guinea pig ileum longitudinal smooth muscle (pKi 10.2), or guinea pig cultured colonic myocytes (pKi 10.3). In all assays MEN16132 was as potent as the peptide antagonist Icatibant, and from 3- to 100-fold more potent than the reference nonpeptide antagonists FR173657 or LF16-0687. The selectivity for the bradykinin B2 receptor was checked at the human bradykinin B1 receptor (pKi < 5), and at a panel of 26 different receptors and channels. The antagonist potency was measured in functional assays, i.e., in blocking the bradykinin induced inositolphosphates (IP) accumulation at the human (CHO: pKB 10.3) and guinea pig (colonic myocytes: pKB 10.3) B2 receptor, or in antagonizing the bradykinin induced contractile responses in human (detrusor smooth muscle: pKB 9.9) and guinea pig (ileum longitudinal smooth muscle: pKB 10.1) tissues. In both functional assay types MEN16132 exerted a different antagonist pattern, i.e., surmountable at the human and insurmountable at the guinea pig bradykinin B2 receptors. Moreover, the receptor determinants important for the high affinity interaction of MEN16132 with the human bradykinin B2 receptor were investigated by means of radioligand binding studies performed at 24 point-mutated receptors. The results obtained revealed that residues in transmembrane segment 2 (W86A), 3 (I110A), 6 (W256A), and 7 (Y295A, Y295F but not much Y295W), were crucial for the high affinity of MEN16132. In conclusion, MEN16132 is a new, potent, and selective nonpeptide bradykinin B2 receptor antagonist.

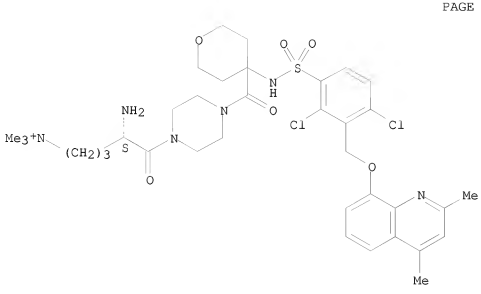
IT 869880-33-1, MEN 16132
RL: DMA (Drug mechanism of action); PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(bradykinin B2 receptor antagonist MEN16132: pharmacol. and mol. characterization)

RN 869880-33-1 CA

CN 1-Piperazinepentanaminium, δ-amino-4-[[4-[[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]tetrahydro-2H-pyran-4-yl]carbonyl]-N,N,N-trimethyl-ε-oxo-, chloride, hydrochloride (1:1:1), (δS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

● Cl⁻

● HCl

REFERENCE COUNT: 34 THERE ARE 34 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 8 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:16847 CA
TITLE: MEN16132, a novel potent and selective nonpeptide kinin B2 receptor antagonist: In vivo activity on bradykinin-induced bronchoconstriction and nasal mucosa microvascular leakage in anesthetized guinea pigs
AUTHOR(S): Valenti, Claudio; Cialdai, Cecilia; Giuliani, Sandro; Lecci, Alessandro; Tramontana, Manuela; Meini, Stefania; Quartara, Laura; Maggi, Carlo Alberto
CORPORATE SOURCE: Department of Pharmacology, Menarini Ricerche, Florence, Italy
SOURCE: Journal of Pharmacology and Experimental Therapeutics (2005), 315(2), 616-623
CODEN: JPETAB; ISSN: 0022-3565
PUBLISHER: American Society for Pharmacology and Experimental Therapeutics
DOCUMENT TYPE: Journal

LANGUAGE: English

AB We have tested the activity of 4-(S)-amino-5-(4-{4-[2,4-dichloro-3-(2,4-dimethyl-8-quinolyloxymethyl)phenylsulfonamido]-tetrahydro-2H-4-pyranylcarbonyl} piperazino)-5-oxopentyl(trimethyl)ammonium chloride hydrochloride (MEN16132), a novel nonpeptide kinin B2 receptor antagonist, on bradykinin (BK)-induced inflammatory responses, bronchoconstriction, and hypotension in guinea pigs. After i.v. (1-10 nmol/kg i.v.), intratracheal (i.t.) (10-100 nmol/kg i.t.), or aerosol (0.01-0.1 mM/5 min) administration, MEN16132 inhibited in a dose-dependent manner the bronchoconstriction induced by BK (10 nmol/kg i.v.). MEN16132 was more potent and possessed a longer duration of action as compared with the peptide B2 receptor antagonist icatibant (HOE140; H-D-Arg-Arg-Pro-Hyp-Gly-Thi-Ser-D-Tic-Oic-Arg-OH trifluoroacetate). After i.v. administration, its inhibitory effect on bronchoconstriction lasted more than 8 h at 30 nmol/kg. When administered by i.v. or i.t. routes, the dose completely inhibiting bronchoconstriction also partially reduced the hypotensive response to BK, whereas after aerosol administration, the inhibitory effect was limited to respiratory level. Intranasal (i.n.) administration of MEN16132 (0.01-0.3 nmol/nostril) reduced, in a dose-dependent and long-lasting manner, the nasal mucosa plasma protein extravasation induced by BK (100 nmol/nostril), and it exerted a complete inhibition at about 30-fold lower dose than icatibant. At 1 nmol/nostril, MEN16132 activity was significant for at least 6 h with no systemic effect measured as inhibition of BK-induced hypotension, and at 10 nmol/nostril, the inhibitory effect lasted for more than 15 h with only a weak effect on hypotension. These findings indicate that in vivo MEN16132 is a potent kinin B2 receptor antagonist with long duration of action, both after i.v. and local administration. A complete and prolonged inhibition of BK-induced bronchoconstriction or nasal inflammation can be achieved with MEN16132 topical administration (aerosol or i.n.) at doses devoid of systemic effects.

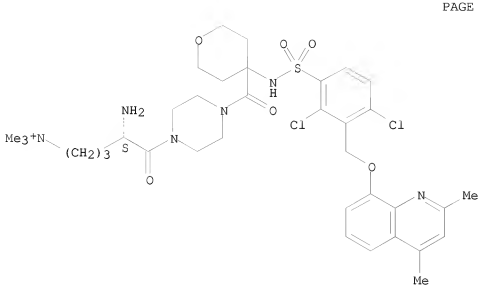
IT 869880-33-1, MEN 16132
RL: PAC (Pharmacological activity); THU (Therapeutic use); BIOL (Biological study); USES (Uses)
(nonpeptide kinin B2 receptor antagonist MEN16132 inhibits bradykinin-induced bronchoconstriction and nasal mucosa microvascular leakage)

RN 869880-33-1 CA

CN 1-Piperazinepentanaminium, δ-amino-4-[[4-[[[2,4-dichloro-3-[[(2,4-dimethyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]tetrahydro-2H-pyran-4-yl]carbonyl]-N,N,N-trimethyl-ε-oxo-, chloride, hydrochloride (1:1:1), (δS)- (CA INDEX NAME)

Absolute stereochemistry.

PAGE 1-A



PAGE 2-A

● Cl⁻

● HCl

REFERENCE COUNT: 36 THERE ARE 36 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L4 ANSWER 9 OF 9 CA COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:42038 CA
TITLE: Basic non-peptide bradykinin antagonists, particularly 3-(8-quinolinoxymethyl)benzenesulfonamide derivatives of α,α-dialkyl amino acids, with specific B2 receptor antagonist activity, and pharmaceutical compositions therefrom
INVENTOR(S): Calvani, Frederico; Catrambone, Fernando; Felicetti, Patrizia; Fincham, Christopher Ingo; Giolitti, Alessandro; Maggi, Carlo Alberto; Quartara, Laura; Rossi, Cristina; Terracciano, Rosa
PATENT ASSIGNEE(S): Menarini Ricerche S.P.A., Italy
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003103671	A1	20031218	WO 2003-EP5893	20030605
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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IT 2002MI1247	A1	20031209	IT 2002-MI1247	20020607
CA 2488565	A1	20031218	CA 2003-2488565	20030605
AU 2003242628	A1	20031222	AU 2003-242628	20030605
BR 2003011825	A	20050315	BR 2003-11825	20030605
EP 1513531	A1	20050316	EP 2003-757025	20030605
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CN 1658877	A	20050824	CN 2003-813027	20030605
JP 2005532354	T	20051027	JP 2004-510790	20030605
MX 2004PA12193	A	20050225	MX 2004-PA12193	20041206
US 20060205712	A1	20060914	US 2005-516681	20050711
PRIORITY APPLN. INFO.:			IT 2002-MI1247 A	20020607
			WO 2003-EP5893 W	20030605
OTHER SOURCE(S):	MARPAT 140:42038			

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Non-peptide compds. of formula I, having activity as specific antagonists of bradykinin (BK) B2 receptor, are disclosed [wherein: R1 = H or C1-4 alkyl; R2, R3 = C1-4 alkyl; or R2 and R3 form a 3- to 7-membered (hetero)cyclic aliphatic group with 0-2 N/O/S atoms; R4, R5 = H, C1-4 alkyl; X = halo, OR1, SR1, CN, or C1-4 alkyl; B = variety of groups with at least 1 amino group of basic character or a tetraalkylammonium group, typically with 1 or 2 such groups, selected from particular cyclic and acyclic structures; including particular pharmacol. acceptable salts with (in)organic acids, and including optical isomers and their (non)racemic mixts.]. Compds. I are chemical characterized by the presence of an alpha,alpha-disubstituted amino acid residue, and at least one addnl. amino group, free or salified, or the corresponding ammonium quaternary salt. I are a novel class of medicaments, which can be used in treating a variety of disorders in which B2 receptors are involved. Approx. 90 example compds. and approx. 20 intermediates are described. For instance, invention compound II was prepared as the trifluoroacetate salt in 26% yield by EDC coupling of a Boc-protected aminohexanoic acid derivative with the corresponding piperazine derivative, followed by deprotection. In a test for binding to human B2 receptor expressed in human fibroblasts W138, invention compound III had a pKi of 10.1. Compds. I also inhibited bradykinin-induced bronchospasm in guinea pigs (no data), showing a higher potency and longer duration than similar mols. not containing the

α,α-dialkyl amino acid moiety.

IT 635694-96-1P, N-[2-[4-(2-(S)-Amino-6-dimethylaminohexanoyl)piperazin-1-yl]-1,1-dimethyl-2-oxoethyl]-2,4-dichloro-3-(2-methylquinolin-8-yloxymethyl)benzenesulfonamide trifluoroacetate
RL: PAC (Pharmacological activity); SPN (Synthetic preparation); THU (Therapeutic use); BIOL (Biological study); PREP (Preparation); USES (Uses)
(drug candidate; preparation of (quinolinoxymethyl)benzenesulfonamide derivs. of α,α-dialkyl amino acids as non-peptide, B2-selective bradykinin antagonists)

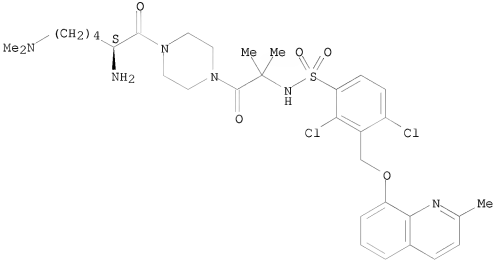
RN 635694-96-1 CA

CN Piperazine, 1-[(2S)-2-amino-6-(dimethylamino)-1-oxohexyl]-4-[2-[[[2,4-dichloro-3-[[(2-methyl-8-quinolinyl)oxy]methyl]phenyl]sulfonyl]amino]-2-methyl-1-oxopropyl]-, trifluoroacetate (9CI) (CA INDEX NAME)

CM 1

CRN 635694-95-0
CMF C33 H44 C12 N6 O5 S

Absolute stereochemistry.



CM 2

CRN 76-05-1
CMF C2 H F3 O2

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

=> file marpat

=> d ibib abs fqhit 1-4

L6 ANSWER 1 OF 4 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 144:412540 MARPAT
TITLE: Preparation of piperazine-linked amino acid derivatives with a cyclic group and a quaternary ammonium group in the alpha positions as non-peptide bradykinin antagonists with specific B2 receptor antagonistic activity
INVENTOR(S): Felicetti, Patrizia; Fincham, Christopher Ingo; Giolitti, Alessandro; Maggi, Carlo Alberto; Quartara, Laura; Rossi, Cristina
PATENT ASSIGNEE(S): Istituto Luso Farmaco d'Italia S.p.A., Italy
SOURCE: PCT Int. Appl., 24 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

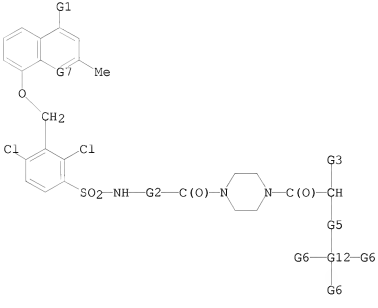
PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2006040004	A1	20060420	WO 2005-EP10412	20050927
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, LY, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SM, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
RW: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG, BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW, AM, AZ, BY, KG, KZ, MD, RU, TJ, TM				
AU 2005293881	A1	20060420	AU 2005-293881	20050927
CA 2583920	A1	20060420	CA 2005-2583920	20050927
EP 1799214	A1	20070627	EP 2005-789989	20050927
EP 1799214	B1	20071226		
R: AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LI, LT, LU, LV, MC, NL, PL, PT, RO, SE, SI, SK, TR, AL, BA, HR, MK, YU				
CN 101039671	A	20070919	CN 2005-80034833	20050927
AT 381931	T	20080115	AT 2005-789989	20050927
US 20070281944	A1	20071206	US 2007-786041	20070410
IN 2007KN01295	A	20070720	IN 2007-KN1295	20070412
PRIORITY APPLN. INFO.:			IT 2004-MI1963	20041015
			WO 2005-EP10412	20050927

GI

* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Non-peptide compds. I, which have activity as specific antagonists of bradykinin (BK) B2 receptor and can be used in treating a variety of conditions in which activation of B2 receptors is involved, are disclosed [wherein: R = H or methyl; W = single bond or O; n = 3 or 4; X = H or (un)substituted amino; Y = quaternary ammonium group, and pharmaceutically acceptable salts, enantiomers and enantiomeric mixts. thereof]. For instance, ammonium chloride II was prepared as a dihydrochloride salt in multiple steps from 2,6-dichlorotoluene, 4-aminotetrahydropyran-4-carboxylic acid, 2,4-dimethyl-8-quinolinol, N-Bocpiperazine and Boc-Orn-OH. Biol. assays showed that the invented compds. have higher binding affinity in vivo (pKi = 10.3 for II) and stronger antagonistic activity in vitro (pA2 = 10.3 for II) than the structurally related analogs of patent WO03103671.

MSTR 1



G2 = 36

G7 = N
Patent location: claim 1
Note: and pharmaceutically acceptable salts
Stereochemistry: and enantiomers

REFERENCE COUNT: 3 THERE ARE 3 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 2 OF 4 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 141:395802 MARPAT
TITLE: Preparation of substituted phenylalkanoic acids, including amino acid derivatives
INVENTOR(S): Van Zandt, Michael C.; Fang, Haiquan; Hu, Shaojing; Whitehouse, Darren
PATENT ASSIGNEE(S): The Institutes for Pharmaceutical Discovery, LLC, USA
SOURCE: PCT Int. Appl., 131 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2004092146	A2	20041028	WO 2004-US11650	20040414
WO 2004092146	A3	20041229		
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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AU 2004231106	A1	20041028	AU 2004-231106	20040414
CA 2522080	A1	20041028	CA 2004-2522080	20040414
US 20040248937	A1	20041209	US 2004-824057	20040414
EP 1633354	A2	20060315	EP 2004-750170	20040414
EP 1633354	B1	20080123		
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IT, LI, LU, NL, SE, MC, PT, IE, SI, LT, LV, FI, RO, MK, CY, AL, TR, BG, CZ, EE, HU, PL, SK, HR				
BR 2004009447	A	20060418	BR 2004-9447	20040414
CN 1794989	A	20060628	CN 2004-80014576	20040414
JP 2006524248	T	20061026	JP 2006-510073	20040414
AT 384526	T	20080215	AT 2004-750170	20040414
NO 2005004769	A	20060103	NO 2005-4769	20051017
IN 2005KN02090	A	20061117	IN 2005-KN2090	20051024
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			WO 2004-US11650	20040414

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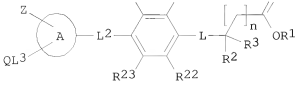


I

AB The invention relates to compds. I [n is 0-3; R1 is H, alkyl, phenylalkyl or alkenyl; R2 is Ph, phenylalkyl, alkyl, carbamoylalkyl, alkylsulfonylalkyl, heterocycloalkyl, etc.; R3 is H or CO2R1; R20-R23 are independently H, arylalkoxy, arylalkyl, halo, alkyl, OH, alkoxy, NO2, NH2, alkylamino, etc.; L is SO2NH, sulfonyl(alkylimino), NHSO2, O, CONH, carbonyl(alkylimino), SO2, carbonylalkylene, alkylenecarbonyl, NH or alkylimino (the alkyl group are optionally substituted with Ph or substituted phenyl); L2 is a bond, CONR9, NR9CO, alkylene-CONR9, NR9, etc. (R9 is H or alkyl optionally substituted with CO2H, arylsulfonyl or arylalkyl); ring A is (un)substituted Ph, naphthyl, thiazolyl, pyrazolyl, furanyl, dihydropyrazolyl, benzofuranyl, dibenzofuranyl, pyrimidyl, pyridyl, quinolinyl, naphthyl, quinazolinyl, benzo[b]thiophene, imidazolyl, isothiazolyl, pyrrolyl, oxazolyl or triazolyl; Q is H, aryl, arylcarbonylaryl, alkyl, halo, etc.; L3 is a bond, alkyleneoxy, oxyalkylene, alkylene, alkenylene or CO; Z is absent, H, aroylamino, (un)substituted Ph or cycloalkylcycloalkanoyl(alkyl)amino] and their pharmaceutically-acceptable salts, which are useful in the treatment of metabolic disorders related to insulin resistance or hyperglycemia. These compds. include inhibitors of protein tyrosine phosphatase (PTP-1B) that are useful in the treatment of diabetes and other PTP-1B mediated diseases such as cancer and neurodegenerative diseases. Thus, 2-[4-[4-(4-chlorophenyl)-5-(4-ethylphenyl)thiazol-2-ylcarbamoyl]benzenesulfonylamino]-3-phenylpropionic acid was prepared by cyclocondensation of 4-ClC6H4COCH2C6H4Et-4 (preparation given) with thiourea, acylation with 4-ClSO2C6H4CO2H, and coupling with phenylalanine tert-Bu ester hydrochloride. The product was shown to increase the glucose infusion rate in rats at 30 mg/kg.

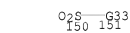
MSTR 1

G1 = quinolinyl
G2 = 83-1 84-4

G3 = m-C6H4 (opt. substd. by G20)
G4 = 136-2 139-5

G17 = 124-1 125-84 / 126-1 127-84

G20 = alkoxy (opt. substd. by 1 or more aryl)
G26 = O
G30 = (0-3) CH2
G31 = 150-2 151-137



G33 = NH
G39 = alkylene <containing 1-6 C>
Patent location: claim 1
Note: substitution is restricted
Note: additional substitution also claimed
Note: or pharmaceutically acceptable salts

L6 ANSWER 3 OF 4 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 140:42038 MARPAT
TITLE: Basic non-peptide bradykinin antagonists, particularly 3-(8-quinolinoxymethyl)benzenesulfonamide derivatives of α,α-dialkyl amino acids, with specific B2 receptor antagonist activity, and pharmaceutical compositions therefrom
INVENTOR(S): Calvani, Frederico; Catrambone, Fernando; Felicetti, Patrizia; Fincham, Christopher Ingo; Giolitti, Alessandro; Maggi, Carlo Alberto; Quartara, Laura; Rossi, Cristina; Terracciano, Rosa
PATENT ASSIGNEE(S): Menarini Ricerche S.P.A., Italy
SOURCE: PCT Int. Appl., 81 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: English
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 2003103671	A1	20031218	WO 2003-EP5893	20030605
W: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW				
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IT 2002MI1247	A1	20031209	IT 2002-MI1247	20020607
CA 2488565	A1	20031218	CA 2003-2488565	20030605
AU 2003242628	A1	20031222	AU 2003-242628	20030605
BR 2003011825	A	20050315	BR 2003-11825	20030605

EP 1513531	A1	20050316	EP 2003-757025	20030605	
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CN 1658877	A	20050824	CN 2003-813027	20030605	
JP 2005532354	T	20051027	JP 2004-510790	20030605	
MX 2004PA12193	A	20050225	MX 2004-PA12193	20041206	
US 20060205712	A1	20060914	US 2005-516681	20050711	
PRIORITY APPLN. INFO.:			IT 2002-MI1247	20020607	
			WO 2003-EP5893	20030605	

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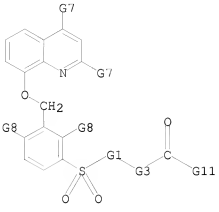
* STRUCTURE DIAGRAM TOO LARGE FOR DISPLAY - AVAILABLE VIA OFFLINE PRINT *

AB Non-peptide compds. of formula I, having activity as specific antagonists of bradykinin (BK) B2 receptor, are disclosed [wherein: R1 = H or C1-4 alkyl; R2, R3 = C1-4 alkyl; or R2 and R3 form a 3- to 7-membered (hetero)cyclic aliphatic group with 0-2 N/O/S atoms; R4, R5 = H, C1-4 alkyl; X = halo, OR1, SR1, CN, or C1-4 alkyl; B = variety of groups with at least 1 amino group of basic character or a tetraalkylammonium group, typically with 1 or 2 such groups, selected from particular cyclic and acyclic structures; including particular pharmacol. acceptable salts with (in)organic acids, and including optical isomers and their (non)racemic mixts.]. Compds. I are chemical characterized by the presence of an alpha,alpha-disubstituted amino acid residue, and at least one addnl. amino group, free or salified, or the corresponding ammonium quaternary salt. I are a novel class of medicaments, which can be used in treating a variety of disorders in which B2 receptors are involved. Approx. 90 example compds. and approx. 20 intermediates are described. For instance, invention compound II was prepared as the trifluoroacetate salt in 26% yield by EDC coupling of a Boc-protected aminohexanoic acid derivative with the corresponding piperazine derivative, followed by deprotection. In a test for binding to human B2 receptor expressed in human fibroblasts W138, invention compound III had a pKi of 10.1. Compds. I also inhibited bradykinin-induced bronchospasm in guinea pigs (no data), showing a higher potency and longer duration than similar mols. not containing the α,α-dialkyl amino acid moiety.

MSTR 1



G1 = NH
G3 = 34

34

G8 = OH
Patent location: claim 1
Note: also incorporates claims 8 and 9

REFERENCE COUNT: 5 THERE ARE 5 CITED REFERENCES AVAILABLE FOR THIS RECORD. ALL CITATIONS AVAILABLE IN THE RE FORMAT

L6 ANSWER 4 OF 4 MARPAT COPYRIGHT 2008 ACS on STN
ACCESSION NUMBER: 126:131387 MARPAT
TITLE: Benzenesulfonamide derivatives used as bradykinin antagonists
INVENTOR(S): Dodey, Pierre; Pruneau, Didier; Paquet, Jean-Luc; Bondoux, Michel; Houziaux, Patrick; Barth, Martine; Ou, Khan
PATENT ASSIGNEE(S): Fournier Industrie Et Sante, Fr.; Dodey, Pierre; Pruneau, Didier; Paquet, Jean-Luc; Bondoux, Michel; Houziaux, Patrick; Barth, Martine; Ou, Khan
SOURCE: PCT Int. Appl., 40 pp.
CODEN: PIXXD2
DOCUMENT TYPE: Patent
LANGUAGE: French
FAMILY ACC. NUM. COUNT: 1
PATENT INFORMATION:

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9640639	A1	19961219	WO 1996-FR845	19960605
W: JP, US				
RW: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE				
FR 2735128	A1	19961213	FR 1995-6703	19950607
FR 2735128	B1	19970725		
EP 773932	A1	19970521	EP 1996-920901	19960605

EP 773932 B1 20010926
R: AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE
JP 10504840 T 19980512 JP 1996-500190 19960605
AT 206114 T 20011015 AT 1996-920901 19960605
ES 2164896 T3 20020301 ES 1996-920901 19960605
PT 773932 T 20020328 PT 1996-920901 19960605
US 5968951 A 19991019 US 1997-776544 19970131
PRIORITY APPLN. INFO.: FR 1995-6703 19950607
WO 1996-FR845 19960605
OTHER SOURCE(S): CASREACT 126:131387
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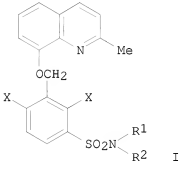
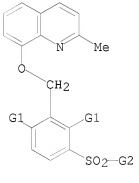


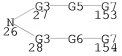
I

AB 3-(Quinolyloxymethyl)benzenesulfonamides I [X = halo; R1 and R2 (same or different) = H or -A-B-R3 [A = linear or branched C1-C12 alkylene, B is a single bond, or a divalent phenylene or substituted indolyl, R3 = H, OH, COR6 (R6 = OH, OMe, OEt), or -NR4R5(R4, R5 (same or different) = H, C1-C4 alkyl), (CH2)nOH, (CH2)nNMe2 or Ac, n = 2-4]] and their salts were prepared and were shown to be bradykinin antagonists.

MSTR 1



G1 = F
G2 = 24 / 26



G3 = alkylene <containing 1-12 C>
G4 = bond
G5 = bond
G6 = bond
G7 = 162

C(O)G11
162

Derivative: and addition salts
Patent location: claim 1

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L2 23 S L1 SAM
L3 339 S L1 FULL

FILE 'CA' ENTERED AT 10:07:29 ON 16 APR 2008
L4 9 S L3

FILE 'MARPAT' ENTERED AT 10:08:00 ON 16 APR 2008
L5 3 S L4
L6 4 S L3 FULL

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